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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/871,610	06/01/2001	Glenn McGall	AFMX-P01-017	1735

42145 7590 02/16/2005

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EXAMINER	
FORMAN, BETTY J	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 02/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/871,610	MCGALL ET AL.	
	Examiner	Art Unit	
	BJ Forman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 2 December 2004 in which Claims 14-15 were amended and the previous rejections were traversed. Applicant's arguments have been thoroughly reviewed and are discussed below.

The previous rejections in the Office Action dated 4 September 2004 under 35 U.S.C. 112, second paragraph are withdrawn in view of the amendments. The previous rejections under 35 U.S.C. 103(a) are maintained.

Claims 1-15 are under prosecution.

Claim Rejections - 35 USC §103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-15 are rejected as obvious over Winkler et al (U.S. Patent No. 5,885,837, issued 23 March 1999) and Goldberg et al (U.S. Patent No. 5,959,098, issued 28 September 1998).

Regarding Claim 1, Winkler et al disclose a method of preparing a nucleic acid array on a support (Column 1, line 64-66), the method comprising: activating a region of the support,

attaching a nucleotide having a masked reactive site linked to a protecting group to a first region and repeating the activating and attaching on other regions of the support. The method further comprising removing the protecting group to provide an unmasked nucleotide, binding an additional nucleotide to the unmasked nucleotide and repeating the removing and binding on regions of the support to prepare a nucleic acid array (Column 9, line 12-Column 10, line 5) wherein the support is rotated about an axis perpendicular to the surface by an amount of from about 20 degrees to a bout 180 degrees, said rotating being prior to, coincident with or subsequent to either binding or attaching steps wherein the support has a different rotational position relative to a previous step (Column 9, lines 39-51). Winkler et al further teach the method wherein the support surface is maintained in a position which permits the reagent fluid to flow through channels during the attaching or binding steps (Column 11, lines 21-65) and the flow path is illustrated as being vertical (Fig. 6a/6b).

Furthermore, Winkler et al specifically teach the flow channels lead "up to the synthesis chamber" (Column 11, lines 42-43) which clearly suggests that the flow channels (of the support) are vertically positioned but they do not specifically teach a vertical position. However, Goldberg et al teach the similar method wherein the surface is maintained in a vertical position during synthesis thereby facilitating removal of bubbles from the cavity which from during the synthesis process (Column 16, lines 13-21). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the vertical positioning of Goldberg et al to the synthesis of Winkler et al for the expected benefit of facilitating bubble removal as taught by Goldberg et al (Column 16, lines 13-21).

Regarding Claim 2, Winkler et al disclose the method wherein the support is rotated subsequent to at least 50% of the attaching or binding i.e. following monomer addition, the substrate is washed and rotated and the monomer addition steps are repeated (Column 9, lines 39-54).

Regarding Claim 3, Winkler et al disclose the method wherein the support is rotated subsequent to at least 80% of the attaching or binding i.e. following monomer addition, the substrate is washed and rotated and the monomer addition steps are repeated (Column 9, lines 39-54).

Regarding Claim 4, Winkler et al disclose the method wherein the support is rotated from about 75 to about 105 degrees i.e. 0 to 180 (Column 10, lines 40-45).

Regarding Claim 5, Winkler et al disclose the method wherein the support is rotated in an amount of about 90 degrees i.e. 0 to 180 (Column 10, lines 40-45 and Column 14, lines 9-10).

Regarding Claim 6, Winkler et al disclose the method wherein the support is vertical (see above discussion regarding Claim 1) and rotated in an amount of about 90 degrees i.e. 0 to 180 (Column 10, lines 40-45 and Column 14, lines 9-10).

Regarding Claim 7, Winkler et al disclose the method wherein the support is a "substantially" square planar silica chip (Column 5, lines 18-26; Column 7, lines 6-7; Column 8, lines 42-54) wherein the support is vertical (see above discussion regarding Claim 1) and rotated in an amount of about 90 degrees i.e. 0 to 180 (Column 10, lines 40-45 and Column 14, lines 9-10).

Regarding Claim 8, Winkler et al do not teach the chip is held with one of four vertices pointing downward. However, Goldberg et al teach the similar method wherein the chip is held vertically, with one of four vertices pointing downward (Fig. 6B) whereby bubble removal is facilitated (Column 16, lines 13-21). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the vertical positioning of Goldberg et al to the synthesis of Winkler et al for the expected benefit of facilitating bubble removal as taught by Goldberg et al (Column 16, lines 13-21).

Regarding Claim 9, Winkler et al disclose the method wherein at least 10 different nucleic acids are synthesized on the surface (Column 10, lines 52-60).

Regarding Claim 10, Winkler et al disclose the method wherein at least 100 different nucleic acids are synthesized on the surface (Column 10, lines 52-60).

Regarding Claim 11, Winkler et al disclose the method wherein at least 1000 different nucleic acids are synthesized on the surface (Column 10, lines 52-60).

Regarding Claim 12, Winkler et al disclose the method wherein at least 10,000 different nucleic acids are synthesized on the surface (Column 10, lines 52-60).

Regarding Claim 13, Winkler et al disclose the method wherein at least 100,000 different nucleic acids are synthesized on the surface (Column 10, lines 52-60).

Regarding Claim 14, Winkler et al disclose the method wherein each localized area is less than about 1 cm^2 (Column 5, lines 36-51).

Regarding Claim 15, Winkler et al disclose the method wherein each localized area is less than about 1 mm^2 (Column 5, lines 36-51).

Response to Arguments

4. Applicant asserts there is no motivation to combine the teachings of Winkler and Goldberg. As evidence for the assertion, Applicant states that Winkler does not teach bubble formation is problematic and therefore, one of skill would not have identified the problem. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the argument is not found persuasive because Goldberg specifically teaches the bubble formation problem and the problem's solution (e.g. Column 16, lines 13-21). Hence, one of ordinary skill in the art of array production would have been motivated to avoid bubble formation problems based on the teaching of Goldberg.

Applicant further asserts that Goldberg teaches positioning of the inlet/outlet ports is the solution to bubble regulation rather than vertical positioning of the substrate as suggested by the office. The argument has been but is not found persuasive because Goldberg specifically teach vertical positioning of the substrate (Column 16, line 18) wherein the combination of inlet/outlet port positioning on the vertical substrate facilitated bubble removal. The fact that the port positioning is important, does not negate the fact that vertical positioning is also a component of the bubble problem solution.

5. Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamble et al (U.S. Patent No. 5,981,733, issued 9 November 1999) and Winkler et al (5,677,195, issued 14 October 1997).

Regarding Claim 1, Gamble et al disclose a method of preparing a nucleic acid array on a support wherein each nucleic acid occupies a separate known region of the support said synthesis comprising: activating a region of the support, attaching a nucleotide to a first region, said nucleotide having a masked reactive site linked to a protective group, repeating steps of activating and attaching on other regions of the support whereby each of said other regions has bound thereto another nucleotide comprising a masked reactive site wherein said another nucleotide may be the same of different from that used in the first step, removing the protecting group from one of the nucleotides bound to one of the regions of the support to provided a region bearing a nucleotide having an unmasked reactive site, binding an additional nucleotide to the nucleotide with an unmasked reactive site, and repeating the steps of removing and binding until a desired plurality of nucleic acids is synthesized, each occupying a separate known region wherein the surface of the substrate is maintained in a position which is vertical or about 30 degrees of vertical and wherein the substrate is rotated around an axis

perpendicular to said surface by an amount of from about 20 degrees to about 180 degrees, said rotating being done prior to and subsequent to at least one of said attaching and binding steps (Column 12, line 18-Column13, line 54 and Claims 9 & 10) whereby said rotated support has a different position relative to the support in the prior attaching step (i.e. moved along the X-Y axis, Column 12, lines 52-54) and wherein at least one of said attaching or binding steps occurs after the support is rotated i.e. during synthesis, the support is cyclically moved between the jetting system and the reaction chamber, Column 5, lines 66-67).

Gamble et al further teach the method wherein the support is held in a vertical position for reagent delivery (Column 4, lines 21-34) whereby the entire surface of the substrate is coated with the reagent and wherein the reagents include any reagents necessary for synthesis (Column 4, lines 40-46) whereby the substrate is in a vertical position during activation step (a) and clearly suggests that the substrate may be in a vertical position during attachment step (b). Furthermore, Gamble et al clearly provide motivation to position the substrate in vertical position during the attachment step when they teach that a vertical position provides complete coverage of the activated area and eliminates bubbles in the reagent solution (Column 4, lines 21-34). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to vertically position the substrate of Gamble et al during the attachment step to thereby insure complete coverage of the activated area and to eliminate problematic bubbles as they desire (Column 4, lines 21-34).

Gamble et al teach the method wherein the rotated support has a different position relative to the support in the prior attaching step (i.e. moved along the X-Y axis, Column 12, lines 52-54) but they do not teach the rotated position is different from the previous attachment/binding step. However, Winkler et al teach a similar method comprising activating a region of the support, attaching a nucleotide having a masked reactive site linked to a protecting group to a first region, removing the protecting group to provide an unmasked nucleotide, binding an additional nucleotide to the unmasked nucleotide and repeating the

removing and binding on regions of the support to prepare a nucleic acid array (Column 15, line 10-Column 16, line 21) wherein the support is rotated about an axis perpendicular to the surface by an amount of from about 20 degrees to a bout 180 degrees, said rotating being prior to, coincident with or subsequent to either binding or attaching steps wherein the support has a different rotational position relative to a previous step (Column 15, lines 53-67) to thereby produce different flow patterns across the substrate. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the rotation of Gamble et al with the rotation providing a different rotational position relative to the previous attachment/binding step of Winkler et al for the expected benefit of producing different flow patterns across the substrate as desired by Winkler et al (Column 15, lines 53-67).

Regarding Claims 2 & 3, Gamble et al disclose the method wherein said rotating is conducted prior to or subsequent to at least 50% (Claim 2) and at least 80% (Claim 3) of said attaching and binding (Column 12, line 18-Column19, line 54 and Claim 9).

Regarding Claims 4 & 5, Gamble et al disclose the method wherein said rotating in an amount of from about 70 to about 105 degrees (Claim 4) and of about 90 degrees (Claim 5) (Column 12, line 18-Column19, line 54 and Fig. 12).

Regarding Claim 6, Gamble et al disclose the method wherein the interface is vertical (i.e. the support is vertical) and said rotating is an amount of about 90 degrees (Column 12, line 18-Column19, line 54; Claims 9 & 10; and Fig. 12).

Regarding Claim 7, Gamble et al teach the method wherein the substrate is square and a surface of the substrate (i.e. interface) is maintained in a position which is vertical or about 10 degrees of vertical (Column 12, line 18-Column19, line 54 and Claims 9 & 10) but they do not teach the substrate is substantially square silica chip. Winkler et al teach the similar method wherein the support is a "substantially" square planar silica chip (Column 14, lines 45-55) wherein the support rotated in an amount of about 90 degrees i.e. 0 to 180 (Column 15, lines 53-56 and Column 29, lines 3-5).

Regarding Claim 8, Gamble et al teach the method wherein the it is preferable that the substrate be positioned so that the maximal surface area of the substrate is covered by fluid rising from the bottom inlet port (Column 4, lines 21-34) but they do not teach the substrate held with one of the four vertices pointing downward. However, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the position of their substrate such that one of the vertices is pointing downward thereby maximizing the surface area covered by fluid rising across the surface for the obvious benefits of coving the entire surface of the substrate as they desire (Column 4, lines 30-34).

Regarding Claims 9-13, Gamble et al teach a method of preparing a nucleic acid array on a support wherein each nucleic acid occupies a separate known region of the support (Column 12, line 18-Column19, line 54 and Claims 9 & 10) and wherein each nucleic acid region have center-to-center spacing of 50 microns to 2 millimeters (Column 10, lines 12-15 and Column 12, lines 21-24) but they do not specifically teach the substrate comprises at least 10 different nucleic acids (Claim 9); at least 100 different nucleic acids (Claim 10); at least 1,000 different nucleic acids (Claim 11); at least 10,000 different nucleic acids (Claim 12); at least 100,000 different nucleic acids (Claim 13). However, high density arrays were well known in the art at the time the claimed invention was made as taught by Winkler et al teach their similar method wherein at least 100,000 different nucleic acids are synthesized on the surface (Column 17, lines 49-57). Winkler et al further teach the need exists for these high-density arrays (Column 1, lines 12-20). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the high density array of Winkler et al to the array synthesis of Gamble et al based on the need for such arrays as taught by Winkler et al (Column 1, lines 12-20).

Regarding Claim 14, Gamble et al disclose the method wherein each different nucleic acid is in a region having an area of less than about 1 cm^2 (Column 10, lines 12-15 and

Column 12, lines 21-24) and Winkler et al disclose the method wherein each localized area is less than about 1 cm^2 (Column 7, lines 10-24).

Regarding Claim 15, Winkler et al disclose the method wherein each localized area is less than about 1 mm^2 (Column7, lines 10-24).

Response to Arguments

6. Applicant asserts there is no prima facie case of obviousness based on the cited art because there is no motivation or suggestion to combine the teachings of Winkler and Gamble. As evidence for the assertion, Applicant states that Gamble does not comment of flow channels or flow patterns, thereby suggesting that these elements are not relevant to the methods of Gamble. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the argument is not found persuasive because Winkler specifically teaches that different flow patterns are desired in the methods of array production (Column 15, lines 53-67). Therefore, one of ordinary skill in the art of array production would have been motivated to apply the teachings of Winkler to the array production of Gamble.

Applicant argues that the office uses overly broad analysis of Winker and Gamble when stating the principle operations of both are synthesis of arrays. Applicant asserts that the principle operation of Gamble involves reagent delivery by flowing reagents over the entire surface of the substrate while in contrast, the principle operation of Winkler involves reagent delivery by flowing reagents through channels. Applicant asserts that one of ordinary skill would readily appreciate this difference in principle and therefore, not be motivated to combine the teachings. The argument has been considered but is not found persuasive because, even

if a narrower analysis of the references is considered, both are concerned with reagent flow over a surface to synthesis an array. While Winkler flows reagents over channel surfaces, Gamble also flows over a surface. Hence, both share the same principle of operation i.e. array synthesis by flowing reagents over a surface.

Applicant asserts that if the substrate of Gamble was rotated as claimed, the device of Gamble would be unsuited for its intended purpose. Applicant points to Fig. 7 of Gamble and asserts that rotation of the substrate would prevent mating of the substrate and reaction chamber and therefore one of ordinary skill in the art would not have had a reasonable expectation of success in the modification suggested by the office. The argument has been considered but is not found persuasive. Even if Applicant's analysis of Fig. 7 is correct, the instant claims require rotation of about 20 to about 180 degrees. Assuming the substrate is a rectangle, as illustrated in Fig. 4, rotation of the substrate 180 degrees (as claimed) would provide mating between the substrate and reaction chamber. Therefore, in contrast to Applicant's assertion, the rotation of Gamble's substrate as claimed would not alter the intended purpose of their method and device or require reconstruction of the device.

7. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (571) 272-0741. The examiner can normally be reached on 6:00 TO 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

BJ Forman, Ph.D.
Primary Examiner
Art Unit: 1634
February 16, 2005